REMARKS

Entry of the Amendment and reconsideration of the claims is respectfully requested.

Claims 1-51 have been cancelled without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of these claims in one or more continuation applications.

New claim 52-87 has been added. Support for new claims can be found throughout the specification including at page 13, lines 3-27; page 19, line 26; page 21, line 4; page 22, line-24; and pages 95, line 25 to page 98, line 4.

Rejections Withdrawn

Applicants acknowledge the withdrawal of the rejection of claims 33-38, 41-47, and 49-51 under 35 U.S.C. 112, first paragraph.

35 U.S.C. § 102

Claim 47 was rejected under 35 U.S.C. § 102(b) as anticipated by Mallender et al. as evidenced by Gulliver et al, for reasons of record. Applicants respectfully traverse this rejection. Claim 47 has been cancelled rendering the rejection of this claim moot. Withdrawal of this rejection is therefore requested.

35 U.S.C. 103

Claims 30-51 were rejected under 35 U.S.C. 103(a) as unpatentable over Reddy et al., Vaughan et al., and Zhu et al., for reasons of record. Applicants have cancelled these claims rendering the rejection of these claims moot. Applicants will discuss this rejection in so far as it might apply to the newly presented claims.

In order to establish a prima facie case of obviousness, three basic criteria must be met, namely: 1) the references when combined must teach or suggest all of the claim limitations; 2) there must be suggestion or motivation to modify the reference or combine the reference teachings, either in the references themselves or in the knowledge generally

available to one of ordinary skill in the art; and 3) a reasonable expectation of success. MPEP 706.02(j). Applicants submit that not all of these requirements have been met, in the least, because the references even when combined do not teach all the limitations of the claims, there is no motivation to combine the references in the manner suggested by the Examiner, and because there would be no reasonable expectation of success in doing so.

Applicants' claims 52-55 are directed to methods and host cells for preparing bispecific antibodies wherein the antibody variable light chain is selected to have a common sequence and the antibody variable light chain domain interacts with a first variable heavy chain domain to form a first binding domain and with a second heavy chain variable domain to form a second binding domain. Applicants' claims 56-65 are directed to methods and host cells for preparing a bispecific antibody wherein each variable light chain has three CDRs and has at least 98% sequence identity with the other variable light chain of the bispecific antibody, and only differ at amino acid positions outside of the CDRs. Claims 66-73 are directed to host cells and methods for preparing a bispecific antibody, wherein the variable light chain is selected to have a common sequence from a first antibody variable light chain specific for a first antigen and from a second antibody variable light chain specific for a second antigen, wherein the first and second antibody bind to different antigens. Claims 74-81 are directed to host cells and methods for preparing a bispecific antibody, wherein the variable light chain has three CDRs and is selected to have at least 98% sequence identity to a first antibody variable light chain specific for a first antigen and from a second antibody variable light chain specific for a second antigen, wherein the first and second antibody bind to different antigens, and wherein the variable light chain polypeptide only differs at amino acid positions outside of the CDRs. Claims 82-87 are directed to a method for preparing a bispecific antibody whereby a variable light chain is obtained by screening a library of antibody variable domains, and selecting said variable light chain to have at least 98% sequence identity to each variable light chain domain of a first and second antibody, wherein the first and second antibody bind to different antigens.

Applicants submit that the cited references, alone or in any combination, do not teach methods of preparing a bispecific antibody as claimed.

1. The references when combined do not teach all of the elements of the claimed invention.

Applicants submit that even when all of the references are combined, they do not disclose all of the elements of the claimed invention. As stated above, the present claims provide for selecting a common light chain for the bispecific antibodies. The Applicants have discovered and disclosed that common light chains can likely be found for any V_L comparison of antibodies directed against different antigens (Example 4). The existence of common light chains allows for methods of preparing bispecific antibodies with greater efficiency by eliminating the mispairing of light and heavy chains.

None of the cited references, alone or in combination, teach selecting a common light chain for the bispecific antibody.

Reddy et al. teaches a method of producing a BsMAb recognizing both CEA and doxorubicin for site-specific drug delivery. This reference does not discuss any problems with the formation of the bispecific antibodies and is not concerned with the pairing of light and heavy chains. Reddy et al. does not teach or suggest a method of forming bispecific antibodies by selecting a common variable light chain, or by selecting variable light chains that have at least 98% sequence identity to one another in amino acid positions outside of CDRs.

The Vaughan et al. reference discloses and is directed to an scFv phage library of naïve antibody variable domains. The reference reports that the same light chain is sometimes paired with different heavy chains in antibodies with different specificities. However, this reference does not teach or suggest that such light chains should be selected over other light chains or that these light chains can or should be used in bispecific antibodies. In addition, Vaughan et al. does not describe or suggest forming a bispecific antibody by selecting variable light chains that have at least 98% sequence identity to one another in amino acid positions outside of CDRs or forming a bispecific antibody comprising a first and second binding domain with the same light chain. Since

this reference does not teach or suggest a method of obtaining bispecific antibodies, the reference does not teach or suggest selecting light chains having at least 98% sequence identity or even 100% sequence identity over other light chains to prepare a bispecific antibody in high yield.

Nor does the Zhu et al. reference remedy these deficiencies. This reference is directed to the use of domain interface engineering strategies to enhance the preference of a pair of single chain Fv proteins to form heterodimers rather than homodimers. Zhu et al. nowhere discuss, however, any problems with the pairing of light and heavy chains. Zhu et al. reference does not teach or suggest a method of forming bispecific antibodies by selecting a common variable light chain, or by selecting variable light chains that have at least 98% sequence identity to one another in amino acid positions outside of CDRs.

Therefore, Applicants submit that none of the references, alone or in any combination, disclose all of the elements of Applicants' claims. The Examiner contends, however, that the Applicants have merely "recognized another advantage which would flow naturally from following the suggestion of the prior art," which "cannot be the basis for patentability when the differences would otherwise be obvious." Applicants respectfully disagree.

Applicants have not in fact merely recognized an advantage that flows naturally from the prior art, because the prior art, even if combined, does not result in a method of preparing bispecific antibodies by selecting the types of common light chains as claimed. As discussed above, none of the references, alone or in combination, recognizes that common light chains as claimed can likely be found for any V_L comparison. Nor do any of the references even teach or suggest the existence of a problem with the mispairing of light and heavy chains, let alone teach or suggest any solution to such a problem. It is the Applicants who have identified a solution to the problem of chain mispairing. Consequently, the present claims are patentable over the cited references, alone or in any combination, for the foregoing reasons.

2. The Examiner has not established a motivation to combine the cited references in the suggested manner.

"A rejection cannot be predicated on the mere identification . . . of individual components of the claimed invention. Rather, particular findings must be made as to the reason the skilled artisan, with no known knowledge of the claimed invention, would have selected these components for combination in the manner claimed." *Ecolochem Inc. v. Southern Calif. Edison Co.*, 227 F3d 1361, 1375 (Fed. Cir. 2000). "Obvious to try" is not the standard. *Id.* at 1374.

Applicants submit that one of skill in the art would not be motivated to combine or modify the references as cited by the Examiner. As discussed previously, the Reddy et al. reference is directed to showing the functionality and dual specificity of specific bispecific antibodies. This reference discloses the preparation of a rodent bispecific antibody against CEA and doxorubicin for therapeutic use. The Examiner contends that one of skill reading Reddy et al. would be motivated to produce a high-affinity human bispecific antibody against CEA and doxorubicin comprising a light chain disclosed by Vaughn et al., because Vaughn et al. teaches a first human antibody fragment that binds doxorubicin, and a second antibody fragment that binds CEA. Applicants respectfully disagree.

There is no discussion in Reddy et al. of any problems with making or using the antibody disclosed therein, or any other bispecific antibody. This reference is not directed to methods for preparing bispecific antibodies, and does not teach or suggest selection of a common variable light chain, or selection of variable light chains that have at least 98% sequence identity to one another in amino acid positions outside of CDRs as a solution to preparing and/or increasing yield of bispecific antibodies.

Vaughn et al. is also not directed to methods of preparing bispecific antibodies. The Vaughan et al. reference is directed to forming a *diverse* scFv phage library of naïve antibody variable domains. This reference does not describe bispecific antibodies or any concerns regarding the methods for producing bispecific antibodies. Nor does this reference teach or suggest use of the disclosed variable light chains in a bispecific antibody. Thus, this reference does not teach or suggest that light chains that have at

least 98% sequence identity or even 100% sequence identity should be selected over other light chains to improve yield of bispecific antibodies.

Therefore, one of skill in the art would simply not be motivated to modify the teachings of Reddy et al. to prepare a bispecific antibody against CEA and doxorubicin comprising light chains disclosed by Vaughn et al, because neither of the references teaches or suggests an advantage to, or desirability of, making such a combination. Applicants respectfully submit that the Examiner is employing an improper "obvious to try" rationale to combine the cited references, rather than establishing a motivation or suggestion in the prior art to make the combination.

3. The references do not provide a reasonable expectation of success in obtaining the claimed invention.

As discussed above, the present claims are directed to methods of preparing bispecific antibodies, comprising selecting light chains having at least 98% sequence identity or 100% sequence identity. None of the cited references teach or suggest the feasibility of employing a screening process to select for light chains having at least 98% sequence identity in a bispecific antibody against any two given antigens.

The Vaughan et al. reference does not teach or suggest selecting light chain variable domains that have 98% sequence identity or even 100% sequence identity in a bispecific antibody. Although the Vaughan et al. reference discloses that the same light chain is sometimes paired with different heavy chains, there is no disclosure in Vaughan et al. that a light chain having at least 98% sequence identity can be found at a high frequency of pairwise combinations of any two antibodies of different specificities. The Zhu et al. reference and the Reddy et al. reference also do not teach or suggest that light chain variable domains that have at least 98% or even a 100% sequence identity between antibodies that have different antigenic specificity occurs at great enough frequency to allow for the selection or identification of such variable light chain domain. One of skill in the art reading the cited references would not know that bispecific antibodies with light chains having at least 98% sequence identity could be produced or identified for any two

antigens. Thus, Applicants submit that even if the references are combined they do not provide a reasonable expectation of success.

Based on the foregoing, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 103 rejection of the claims, because the references when combined do not disclose all of the elements of Applicants' claimed invention, there is no motivation to combine the references cited by the Examiner, and there would be no reasonable expectation of success based on these references a method for preparing a bispecific antibody as claimed.

Request for an Interview

Applicants request an interview with the Examiner and his supervisor upon receipt of these papers. Applicants request that the Examiner call Applicant's representative to schedule such an interview.

Summary

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332-5300

Date: December 17, 2004

Katherine M. Kowalchyk
Reg. No. 36,848
KMK:GJG:sab

23552
PATENT TRADEMARK OFFICE